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09/081,522

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/081,522	05/19/98	BROOKS	P TSRI4190CONI

EXAMINER

HM12/0410

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ART UNIT	PAPER NUMBER
1644	15

1644

DATE MAILED: 04/10/01

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 1/31/01

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 17-170 is/are pending in the application.
Of the above, claim(s) 24-27, 39-63, 81-143, 151-154, 166-169 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 17-23, 28-38, 64-80, 144-150, 155-165, 170 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-421-632/40206

DETAILED ACTION

1. Applicant's election without traverse of Group I and the species αvβ3-specific antibodies in Paper No. 14 is acknowledged.

Claims 17-23, 28-38, 64-80, 144-150, 155-165 and 170 are under consideration as the elected invention and species

Claims 24-27, 39-63, 81-143, 151-154 and 166-169 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species.

Claims 1-16 have been canceled previously.

While it is acknowledged that the following four Groups were set forth in the previous Restriction Requirement (Paper No. 12) and applicant's comments, filed 7/24/00 (Paper No. 11), concerning the distinction between the claimed methods(e.g. inhibiting tissue growth versus inducing solid tumor tissue regression);

It is noted that Groups I / III / IV may be overlapping.

Applicant is invited to clarify the distinctions between Groups I / III / IV .

Restriction to one of the following inventions was required under 35 U.S.C. § 121:

I. Claims 17-23, 28-42, 64-84, 144-150, 155-170; drawn to methods of inhibiting tissue growth in solid tumors.

II. Claims 17, 24-42, 105-145, 152-169; drawn to methods of inhibiting tissue growth in inflamed tissue.

III. Claims 43-63; drawn to methods of inducing solid tumor tissue regression.

IV. Claims 85-104; drawn to methods of inhibiting angiogenesis in a carcinoma.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825 (see the specification at page 10, line 22). However, this application fails to comply with the requirements set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence.

The sequence rules embrace all unbranched nucleotide sequences with ten or more bases and all unbranched non-D amino acids sequences with four or more amino acids.

There does not appear to be SEQ ID NO. for "GRGDS" on page 4 of the instant specification.

Applicant is required to meet the requirements for Sequence Rules.

Applicant is required to identify the nucleotide and amino acid sequences in the specification with SEQ. ID NOS.

3. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention, including the use of αvβ3-specific antibodies.

5. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

6. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

7. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 37, 79, 164 : It is apparent that the LM609 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line / hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

Given the patented claims drawn to the use of the LM609 antibody having ATCC Accession Number HB 9537 in IU.S. Patent No. 5,752,230; the instant claims are considered in compliance with the deposit requirements under 35 USC , first paragraph.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 17-20, 22, 28, 29, 31-38, 64-66, 68, 70, 71, 73-80, 144-147, 149, 155-165 and 170 are rejected under 35 U.S.C. § 102(a) as being anticipated by Kim (WO 93/20229; 1449).

Kim teaches neutralizing antibodies, including humanized and antibody fragments, that bind $\alpha v\beta 3$, including the LM609 antibody, that inhibit binding tumor cells with vitronectin, fibrinogen and von Willebrand factor in vivo, in order to inhibit tumor growth and metastasis because tumor growth depends on cell attachment, (see entire document, including Background of the Invention, Summary of the Invention, and Detailed Description of the Invention; also, see page 6, paragraph 2; page 9, paragraph 2)

Kim also teaches modes of administration and doses of therapeutic antibody alone or in combination with other agents that are effective for the same clinical objective, depending on the type of the disease, the severity and course of the disease in the individual at the discretion of the practitioner (pages 9-10); wherein said modes of administration and doses are encompassed by the claimed methods

Although the reference does not state an "angiogenesis-inhibiting amount" per se; the tumor-inhibiting amount taught by the reference would inherently encompass the "angiogenesis-inhibiting amount" encompassed by the claimed methods.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using the αvβ3-specific antibody LM609.

Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

12. Claim 17-20, 22, 28, 29, 31-35, 37, 64-66, 68, 70, 71, 73-77, 79, 144-147, 149, 155-162, 164 and 170 are rejected under 35 U.S.C. § 102(b) as being anticipated by Cheresh (WO 89/05155; 1449) (see entire document).

Cheresh teach antibodies that bind the RGD-directed adhesion receptor, including the LM609 antibody specificity to inhibit binding of this receptor with vitronectin, fibrinogen and von Willebrand factor in vivo, in order to inhibit tumor growth because tumor growth depends on cell attachment (see entire document, including Therapeutic Methods and Compositions on pages 20-23) .

Here, Cheresh also teach modes of administration and doses of therapeutic antibody compositions to meet the needs of the individual and dependent upon the judgement of the practitioner; wherein said modes of administration and doses are encompassed by the claimed methods.

Although the reference does not teach the "αvβ3" specificity per se; the LM609 inherently binds the αvβ3 specificity encompassed by the claimed methods.

Although the reference does not state an "angiogenesis-inhibiting amount" per se; the tumor-inhibiting amount taught by the reference would inherently encompass the "angiogenesis-inhibiting amount" encompassed by the claimed methods.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using the αvβ3-specific antibody LM609.

Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

13. Claims 17-23, 28-38, 64-80, 144-150, 155-165 and 170 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kim (WO 93/20229; 1449) AND/OR Cheresh (WO 89/05155; 1449) in view of Nicosia et al. (Am. J. Pathol. 138: 829 - 833, 1991; 1449), Nip et al. (J. Clin. Invest. 90: 1406-1413, 1992; 1449) , Folkman et al. (Seminars in Cancer Biology 3: 89-96, 1992; 1449) and art known procedures to treating cancers of interest at the time the invention was made.

Cheresh teach antibodies that bind the RGD-directed adhesion receptor, including the LM609 antibody specificity to inhibit binding of this receptor with vitronectin, fibrinogen and von Willebrand factor in vivo, RGD-mediated adhesion, in order to inhibit tumor growth because tumor growth depends on cell attachment (see entire document, including Therapeutic Methods and Compositions on pages 20-23) .

Here, Cheresh also teach modes of administration and doses of therapeutic antibody compositions to meet the needs of the individual and dependent upon the judgement of the practitioner; wherein said modes of administration and doses are encompassed by the claimed methods.

Kim teaches neutralizing antibodies that bind $\alpha v\beta 3$, including the LM609 antibody, that inhibit binding tumor cells with vitronectin, fibrinogen and von Willebrand factor in vivo, via RGD-mediated adhesion, in order to inhibit tumor growth and metastasis because tumor growth depends on cell attachment, (see entire document, including Background of the Invention, Summary of the Invention, and Detailed Description of the Invention; also, see page 6, paragraph 2; page 9, paragraph 2)

Kim also teaches modes of administration and doses of therapeutic antibody alone or in combination with other agents that are effective for the same clinical objective, depending on the type of the disease, the severity and course of the disease in the individual at the discretion of the practitioner (pages 9-10); wherein said modes of administration and doses are encompassed by the claimed methods

The primary references differ from the claimed methods by not disclosing the term "angiogenesis-inhibiting amounts" and certain conventional modes of administration and targeted cancers known at the time the invention was made in the therapeutic treatment of cancer.

Although the primary references do not state an "angiogenesis-inhibiting amount" per se; the tumor-inhibiting amount taught by the reference would have the expected properties of an "angiogenesis-inhibiting amount" encompassed by the claimed methods; given the teachings of inhibiting tumor growth and metastasis with $\alpha v\beta 3$/ RGD-specific inhibitors, including the LM609 antibody specificity.

Although the primary references do not teach certain modes of administration such as peristaltic administration (e.g.; claims 28, 30, 72, 155) and following surgery to remove a solid tumor (e.g. claims 69, 150) per se ; it would have been readily apparent to one of ordinary skill in the art at the time the invention was made to provide the αvβ3/ RGD-specific inhibitors, including the LM609 to meet the needs of the patient, as these claimed limitations were conventional at the time the invention was made and the prior art teaches treating patients with αvβ3/ RGD-specific inhibitors, including the LM609 in conjunction with conventional therapy.

It is noted that Kim teaches the art known use of recombinant antibodies and antibody fragments, while Cheresh does not. Given the teachings of various antibody αvβ3 antibody antagonists; it would have been obvious to the ordinary artisan to employ various antibody inhibitors, including the conventional antibody fragments (e.g.; claims 23, 36, 78, 163) encompassed by the claimed invention, provided they inhibited αvβ3/ RGD-specific interaction

One of ordinary skill in the art at the time the invention was made would have been motivated to select αvβ3/ RGD-specific inhibitors such as αvβ3-specific antibodies such as the LM609 specificity to inhibit tumor growth and metastasis in combination with conventional therapy to treat cancer. Providing αvβ3-specific antibodies such as the LM609 in "angiogenesis-inhibiting amounts" encompassed by the claimed methods would have been expected; given the prior art teaching of inhibiting tumor growth and metastasis. Also, given the metastatic behavior of various tumors, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply such therapeutic intervention to target various tumor types, including those from bladder, breast, colon or lung.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 17-23, 28-38, 64-80, 144-150, 155-165 and 170??? are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kim (WO 93/20229; 1449) AND/OR Cheresh (WO 89/05155; 1449) in view of art known procedures of treating cancers of interest at the time the invention was made as applied to claims 17-23, 28-38, 64-80, 144-150, 155-165 and 170 above and further in view of .
Nicosia et al. (Am. J. Pathol. 138: 829 - 833, 1991; 1449), Nip et al. (J. Clin. Invest. 90: 1406-1413, 1992; 1449) , Folkman et al. (Seminars in Cancer Biology 3: 89-96, 1992; 1449)

Kim AND/OR Cheresh in view of art known procedures of treating cancers are address above and differ from the claimed methods by not disclosing that the tumor inhibiting amounts of αvβ3 antagonist such as the LM609 antibody were "angiogenesis-inhibiting amounts".

In addition to Cheresh and Kim; Nip et al teach the role of αvβ3-RGD mediated interactions in the metastasis with cancers, including melanoma (see entire document) and the ability to block such interactions via αvβ3/ RGD-specific inhibitors, including the LM609 antibody (see entire document, including the Abstract, Introduction and Discussion).

Nicosia et al. teach inhibiting angiogenesis by a RGD inhibitor (see entire document, including the Abstract).

Although the primary references do not state an "angiogenesis-inhibiting amount" per se; the tumor-inhibiting amount taught by the reference would have the expected properties of an "angiogenesis-inhibiting amount" encompassed by the claimed methods; given the combined teachings of inhibiting tumor growth and metastasis with αvβ3/ RGD-specific inhibitors, including the LM609 and RGD inhibitors inhibit angiogenesis.

Also, it was known at the time the invention was made that angiogenesis was necessary but not sufficient for expansion of tumor population, as taught by Folkman et al. (See entire document, particularly Rationale of anti-angiogenic therapy on page 89).

Folkman et al. Also teach that angiogenesis inhibitors may be administered to cancer patients in conjunction with convention chemotherapy for the control of metastatic disease such as prostate, breast or colon cancer (see page 94, column 1, paragraph 3).

Given the teachings of various antibody αvβ3 antibody antagonists; it would have been obvious to the ordinary artisan to employ various antibody inhibitors, including the conventional antibody fragments (e.g.; claims 23, 36, 78, 163) encompassed by the claimed invention, provided they inhibited αvβ3/ RGD-specific interaction

One of ordinary skill in the art at the time the invention was made would have been motivated to select αvβ3/ RGD-specific inhibitors such as αvβ3-specific antibodies such as the LM609 specificity to inhibit tumor growth and metastasis in combination with conventional therapy to treat cancer. Providing αvβ3-specific antibodies such as the LM609 in "angiogenesis-inhibiting amounts" encompassed by the claimed methods would have been expected; given the prior art teaching of inhibiting tumor growth and metastasis. Also, given the metastatic behavior of various tumors, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply such therapeutic intervention to target various tumor types, including those from bladder, breast, colon or lung.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

PHILLIP GAMBEL

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Technology Center 1600
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